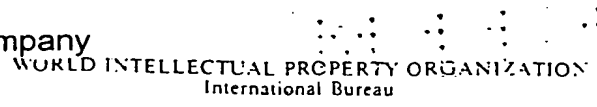


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(54) Title: FLEVOXATE AND DERIVATIVES FOR ERECTILE DYSFUNCTIONS

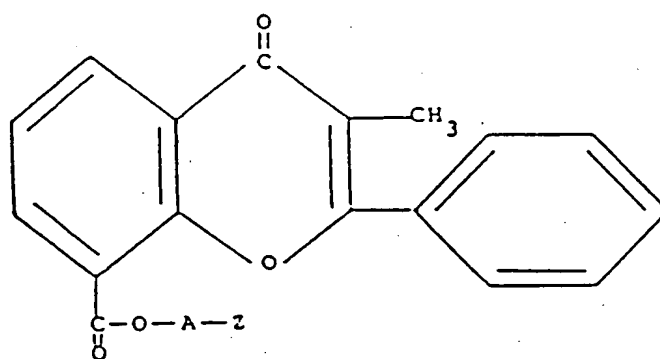
(57) Abstract

Derivatives of 3-methylflavon-8-carboxylic acid are useful for the treatment of penile erectile dysfunctions and for diagnostic methods of erectile impotence.

FLEVOXATE AND DERIVATIVES FOR ERECTILE DYSFUNCTIONS

This invention relates to the use of 3-methyl-flavon-8-carboxylic acid and derivatives thereof for the preparation of a drug for the treatment and for the diagnosis of erectile impotence.

5 In particular, the invention relates to pharmaceutical compositions for the treatment of erectile impotence containing as the active principle 3-methylflavon-8-carboxylic acid or a derivative thereof of formula I



(I)

wherein:

A is a linear or branched C_1 - C_6 alkyl residue and

Z is a dimethylamino, diethylamino, di-n-propylamino, di-

20 isopropylamino, piperidino or morpholino residue,

or pharmaceutically acceptable salts thereof.

Compounds of formula I are known (US Patent No. 2.921.070) and particularly one of them, methylflavone-8-carboxylic acid 2-piperidinoethyl ester (flavoxate) is used
25 in therapy peculiarly for its antispasmodic activity on the smooth muscle of the bladder, ureter and uterus (Ruffmann R., Drug Exp. Clin. Res., 13, 57, (1987)) and it

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has also been shown that Flavoxate accumulates preferentially in the genito-urinary tract (Inoue S. et al., Jyakunin Kenkyu, 6, 260, (1975)). Flavoxate is a very well tolerated drug; the large therapeutic index found in 5 preclinical studies (C. Pietra et al., Il Farmaco Ed. Prat., 41, 267, (1986)) and the absence of serious side effects during clinical application, attest its excellent tolerability. Particularly, cardiocirculatory complications have never been reported. 3-methylflavon-8-carbo-
10 xylic acid(MFCA) is the main metabolite of flavoxate. In terms of pharmacokinetics and - dynamics MFCA is most similar to flavoxate.

Erectile dysfunction is a well known and common disease, of vascular, hormonal, neurogenic or psychogenic
15 origin which causes impaired penile erection.

The insufficient erectile ability of the penis has serious implications for psychological, physical and social well-being of the afflicted individuals. Self confidence in particular, and quality of life in general,
20 are strongly reduced.

Since vascular surgery holds reasonable chances of success only in a limited number of cases, additional attempts to treat this disability have led to various therapeutic approaches. Prosthetic devices that are
25 implanted in the penis to mimic erection or are located outside in the scrotal sac or in an adjacent area to stimulate for instance to transmitting electrical energy to the nervi erigentes. Pharmacological substances which are also injected directly into the corpora cavernosa, where
30 they increase the inflow of blood and consequently

generate tumescence of the penis, are also used.

However, all these methods have evident disadvantages, causing strong psychological apprehensions and also physical discomfort.

5 Among the pharmacological substances, 6,7-dimethoxy-1-veratryl isoquinoline (papaverine) and/or alpha blocking agents (as for example phentolamine) are the most frequently used to induce human penile erection and need to be injected directly into the corpora cavernosa. This
10 procedure has been shown to be most efficient for arteriogenic erectile dysfunctions. Usually the treatment begins with a first injection, performed by a physician as a diagnostic step to differentiate between arteriogenic, psychogenic and the other forms of erectile dysfunctions.
15 In many cases of psychogenic dysfunction this single injection is sufficient to obtain a curative result. If further injections are required, these can be performed either by the physician (office-injection) or by the patient himself (auto-injection).

20 The major drawback of papaverine and/or alpha blockers in erectile dysfunction is the risk of prolonged and painful erection (priapism) which occurs with a certain frequency.

Further serious complications are of cardiocirculatory nature such as arterial hypotension and hypotensive shock which represent typical toxicity of these agents. In
25 some cases fatalities have been reported. Both, papaverine and alpha blockers have a narrow therapeutic index (ratio between the lethal dose and the effective dose), and
30 absolute or relative overdosing can occur especially

during self injections.

Objects and summary of the invention

The shortcomings of available therapeutic modalities as described above are quite evident.

5 Useful pharmaceutical agents for the induction and maintainance of penile erection with low toxicity and easy administration, preferably oral, are strongly and essentially needed and hence are the target of intense research.

10 It has now been found that 3-methylflavon-8-carboxylic acid and compounds of formula I have a relaxing activity on human corpus cavernosum tissue which is comparable to the activity exerted by papaverine during the same experiments. This finding is new and surprising
15 in as much as previously it has been consistently unable to identify any relaxing activity on vascular smooth muscle for flavoxate or MFCA. Any therapeutic activity for erectile dysfunctions has never been reported either.

In fact, numerous investigations in vitro and in
20 vivo, also versus papaverine, had failed to confirm a hypothesized and postulated vasodilating activity of flavoxate. Consequently initial high hopes to develop and market flavoxate as a coronary dilating agent had to be abandoned.

25 On the other side, the absence of a vasodilating activity, resulted in a complete and most beneficial lack of cardiovascular type side effects.

The results obtained in a pharmacological experimentation using flavoxate and MFCA in comparison
30 with papaverine are hereinbelow reported.

5 -



Methods

Human tissue was obtained from patients undergoing penile prosthesis implantation.

Biopsies of human corpus cavernosum tissue were obtained in the operating room and immediately placed in chilled (4°C) physiological salt solution of the following millimolar composition: NaCl 118.3; KCl 4.7; MgSO₄ 0.6; KH₂PO₄ 1.2; CaCl 2.5; NaHCO₃ 25.0; Calcium EDTA 0.026 and glucosio 11.1.

10 The solution is gassed with 95% O₂, 5% CO₂; pH maintained at 7.4 and temperature at 37°C.

Isometric tension measurement

Isometric tension was measured through the experiment with a tension transducer (Grass FTO3, Quincy, 15 MA). The strips of corpus cavernosum were fixed with silk ties on one end to the electrode support and the other end to a wire connected to the force transducer.

The strips were allowed to equilibrate for a period of approximately three hours. The optimal isometric 20 tension for contraction was determined during this period by stepwise stretching of the tissue followed by contraction with 40 mM KCl or 10⁻⁶ M phenylephrine. Whenever the potassium or phenylephrine-induced contraction was within 10% of the previous contraction, 25 that tension was considered optimal for isometric contraction. In all tissues, a standardized three hour equilibration period and isometric tension determination study was utilized. In this fashion, the effect of a molecule on a tissue was able to be compared to the effect 30 of the same molecule on different corpus cavernosum

tissues.

To study contraction, the tissue was maintained at the baseline tension. To study relaxation, the tissue was contracted with different agents.

5 Agents

Drugs were provided in powder form. Stock solutions were made in distilled water. For papaverine and flavoxate the maximal concentration reached 10^{-4} M. At higher concentrations, these molecules would become out of solution. Drugs were introduced to the chamber by cumulative additions in one half log increments.

Calculations

Data is given as means \pm SE. Relaxation are expressed as the percentage relaxation for the maximal relaxation produced by 10^{-3} M sodium nitroprusside.

Results

1) Responses of human corpus cavernosum to papaverine, flavoxate and MFCA at baseline tension.

None of the molecules tested demonstrates any contractile effects of human corpus cavernosum tissue. Two experiments were performed for each molecule.

2a) Responses of human corpus cavernosum (HCC) to papaverine HCl at contracted tension.

Papaverine, at concentration of 10^{-4} M, induced relaxation in HCC contracted with norepinephrine, PG F2 α or potassium. Maximal relaxations to the concentration were: $89.9 \pm 3.1\%$, 90% and $91.6 \pm 1.6\%$ of maximal relaxation, respectively (see figures 1-3). The threshold for the response to this drug was approximately 10^{-5} M.

Typically the relaxation response to papaverine was slow in onset, requiring more than 10 minutes to reach maximal effect (see figure 1). It was difficult to wash out the effect of papaverine. Repeated washes were 5 required before the tissue recovered the ability to contract normally.

2b) Responses of HCC to flavoxate HCl at contracted tension.

Flavoxate, up to 10^{-4} M, induced relaxation of HCC 10 contracted with norepinephrine, PG F2 alpha or potassium. Maximal relaxations to this concentration were: 73.1 +/- 7.7%, 66 +/- 13.2%, and 55.5 +/- 23% of maximal relaxation, respectively (see figures 1-3). The threshold for the response to flavoxate was approximately 3×10^{-5} 15 M. The relaxation response was slow in onset and several minutes were required before the maximal relaxation response to 10^{-4} M flavoxate was achieved.

2c) Responses of HCC to MFCA Na Salt at contracted tension.

20 MFCA was easily put into solution and was tested to a concentration of 3×10^{-4} M. It induced relaxation of HCC contracted with norepinephrine, PG F2 alpha or potassium. Maximal relaxations to 3×10^{-4} M was: 54.2 +/- 5.4%, 92.8 +/- 3.5%, and 62% of maximal relaxation, 25 respectively (see figures 1-3). The threshold of HCC for relaxation by MFCA was 10^{-4} M for norepinephrine and potassium contracted strips and 10^{-5} M for PG F2 alpha contracted tissue.

From what above reported, it is evident how 30 3-methylflavon-8-carboxylic acid and its basic esters of

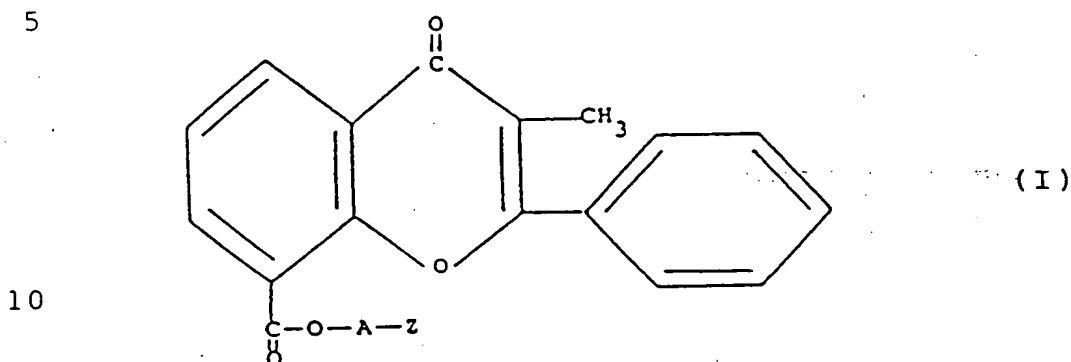
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formula I, particularly flavoxate, may be conveniently used in human therapy for the treatment of erectile impairments. For this purpose, pharmaceutical compositions suited for the oral, topical or parenteral (intracavernous) administration are provided. The oral administration is particularly convenient for its compliance and it is moreover useful as support therapy in patients who otherwise undergo papaverine or alpha-blockers injection. This regimen allows a reduction of the papaverine and alpha-blocker dosage and improves therefore the safe use of these agents. The doses for an effective treatment of erectile impairments will depend on usual factors such as kind and seriousness of the pathology and patient's weight; nevertheless, a daily oral dose of 1.200 mg proved to be generally effective and well-tolerated. Lower dosage are obviously required in case of intracavernous injection. Transdermal administration forms may also be particularly convenient. The preparation of pharmaceutical forms is within the skill of any expert in the field and it is described for instance in Remington's Pharmaceutical Sciences Handbook, Hack Pub. Co., N.Y. USA.

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C L A I M S

1. Use of 3-methylflavon-8-carboxylic acid or a derivative thereof of formula I



wherein:

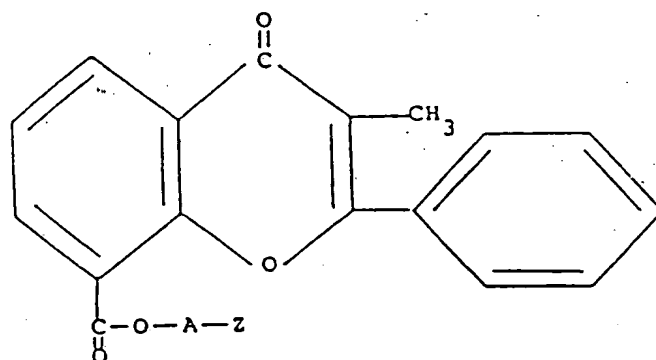
A is a linear or branched C_1-C_6 alkyl residue and
 Z is a dimethylamino, diethylamino, di-n-propylamino,
 15 diisopropylamino, piperidino or morpholino residue,
 or pharmaceutically acceptable salts thereof,
 for the preparation of a medicament for the treatment and
 diagnosis of erectile dysfunctions.

2. The use of 3-methylflavon-8-carboxylic acid or of a
 20 pharmaceutically acceptable salt thereof for the prepara-
 tion of a medicament for the treatment and diagnosis of
 erectile dysfunctions.

3. The use of 2-piperidino-ethyl 3-methylflavon-8-car-
 boxylate or of a pharmaceutically acceptable salt thereof
 25 for the preparation of a medicament for the treatment and
 diagnosis of erectile dysfunctions.

4. Pharmaceutical compositions for the treatment of
 erectile dysfunctions comprising an effective amount of
 3-methylflavon-8-carboxylic acid or of a salt or
 30 derivatives of formula I

5



(I)

wherein:

A is a linear or branched $\text{C}_1\text{-C}_6$ alkyl residue and
10 Z is a dimethylamino, diethylamino, di-n-propylamino, diisopropylamino, piperidino or morpholino residue, or pharmaceutically acceptable salts thereof, in admixture with a suitable carrier.

5. Pharmaceutical compositions according to claim 4,
15 suited for the oral, topical or parenteral administration.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/EP 89/00417

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁴

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC⁴: A 61 K 31/35, A 61 K 31/445, A 61 K 31/535

II. FIELDS SEARCHED

Minimum Documentation Searched ⁷

Classification System

Classification Symbols

IPC⁴

A 61 K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched ⁸

III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
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- | | | |
|---|--|-----|
| Y | Il Farmaco - Ed. Pr., vol. 41, no. 8, 1986,
C. Pietra et al.: "Effects of flavoxate
on urinary bladder contraction, mictu-
rition reflex and urodynamic parameters",
pages 267-273, see page 269, lines
32-40; page 272, lines 4-10
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K.-P. Juenemann et al.: "Hemodynamics
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page 158, left-hand column, lines 5-7;
page 160, left-hand column, lines 26-32
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M. Pavone-Macaluso et al.: "Prostatitis
cronicas", pages 689-700, see page 691,
right-hand column, line 25 - page 692,
left-hand column, line 32; page 697,
right-hand column, lines 1-3
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¹⁰ Special categories of cited documents:

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

16th June 1989

Date of Mailing of this International Search Report

10 JUN. 1989

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

P. C. G. VAN DER PUTTEN

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
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EP. 890-0417.

SA 28006

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The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0266968	11-05-88	AU-A- 8058387 JP-A- 63132825	05-05-88 04-06-88
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